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Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study

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Aims To examine the risk of death associated with antiarrhythmic drug (AAD) therapy in a nationwide unselected cohort of patients with atrial fibrillation (AF).

Methods and results All patients admitted with AF in Denmark from 1995 to 2004 and their subsequent use of AADs were identified by individual-level linkage of nationwide registries. Multivariable Cox proportional-hazard models with time-dependent covariates were used to analyse the risk of death associated with AAD therapy. A total of 141 500 patients were included in the study; of these 3356 (2.4%) patients received treatment with flecainide, 3745 (2.6%) propafenone, 23 346 (16.5%) sotalol, and 10 376 (7.3%) amiodarone. Annualized mortality rates were 2.54, 4.25, 5.29, and 7.42 per year per 100 person years for flecainide, propafenone, sotalol, and amiodarone, respectively. Multivariable Cox proportional-hazard models did not show increased risk of death associated with any of the AADs. Hazard ratio (95% confidence interval) for flecainide 0.38 (0.32–0.44), propafenone 0.65 (0.58–0.71), sotalol 0.65 (0.63–0.67), and amiodarone 0.94 (0.89–1.00).

Conclusion In an unselected cohort of patients with AF, antiarrhythmic treatment with flecainide, propafenone, sotalol, or amiodarone was not associated with increased risk of death. From a safety perspective, this indicates appropriate selection of patients for AAD therapy.

Keywords Antiarrhythmic drug therapy • Atrial fibrillation

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Introduction

Antiarrhythmic drug (AAD) treatment has been associated with increased risk of death in several studies of patients with underlying structural or ischaemic heart disease.[1,2] Consequently, a vigilant focus has been maintained of appropriate selection of patients to receive this potentially harmful therapy, which is often used to treat relatively benign rhythm disturbances such as atrial fibrillation (AF) and other supraventricular tachyarrhythmias. This discussion has become even more relevant after publications of large randomized trials failing to show any mortality benefits of rhythm control over rate control in the treatment of AF.[3–5]

Over the last decade, there has been a shift towards increased use of second and third generation beta-blockers in lieu of primarily sotalol but also of class IC drugs such as flecainide and propafenone.[6] This change may partly reflect a heightened awareness of the proarrhythmic risk posed by these drugs as demonstrated in various trials and reviews.[1,7–9] Whether a significant risk is associated with AAD therapy in a large nationwide unselected population is as yet unresolved. In the present study, we examined the risk of death associated with treatment with flecainide, propafenone, amiodarone, or sotalol among 141 500 patients hospitalized with AF in the period 1995–2004 in Denmark.

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Methods

Population

The cohort of patients selected for this study was identified using the Danish National Patient Registry, a nationwide registry of all hospitalizations in Denmark since 1978. Patients hospitalized with first-time AF [International Classification of Diseases, 10th revision (ICD-10), code I48] as a primary or secondary diagnosis between 1995 and 2004 were identified. All patients alive at discharge were included in the analyses.

Medical treatment

Information on the use of pharmacotherapy was obtained from the Registry of Medicinal Product Statistics (national prescription registry), which includes all prescriptions dispensed from Danish pharmacies since 1995. The national prescription registry also keeps information on date of dispensing, strength, quantity dispensed, and the affiliation of the doctor issuing the prescription. Each prescribed drug is coded according to an international classification of pharmaceuticals, the anatomical therapeutical chemical (ATC) classification. The registry has been found to be accurate and has been described in more detail previously.[10]

All prescriptions of flecainide, propafenone, sotalol, and amiodarone (ATC codes C01BC04, C01BC03, C07AA07, and C01BD01) claimed in the 10-year period from 1995 to 2004 by the study population following the index admission were identified. From all claimed prescriptions, the treatment duration and the mean dosage were calculated for every patient. In order to obtain information concerning concomitant medical treatment, prescriptions claimed, within 180 days before discharge from index admission, of loop diuretics, glucose lowering medication (insulin and oral), statins, digoxin, calcium antagonists, beta-blockers, warfarin, angiotensin-converting enzyme inhibitors, and potassium sparing diuretics were also identified (ATC codes C03C, A10B, C10AA, C01A, C08, C07AB, B01AA03, C09D, C031).

Vital status

Vital status as of the end of December 2004 was obtained from the Civil Registration System.

Comorbidity

We identified diagnoses of comorbidity at the index admission and further enhanced the comorbidity index by identifying diagnoses at admissions up to 1 year prior to the index admission, as done by Rasmussen *et al.*[11] The following comorbidity diagnoses were identified and included in the analyses: ischaemic heart disease (ICD codes I20–I25), chronic heart failure (CHF) (I50), arrhythmias other than AF (I46, I47, I49), cerebrovascular disease (I60–I69), peripheral vascular disease (I70, I74), chronic obstructive pulmonary disease (COPD) (J42–J44), diabetes mellitus (E10–E14), and malignancy (C00–C97) (*Table 1*).

Exposure groups and dosages

Patients were categorized into exposure groups depending on the AAD used at their first prescription claim following the index admission [flecainide, propafenone, sotalol, or amiodarone (*Table 1*)]. The average daily dosage for each patient was calculated as the mean

Table 1 Baseline characteristics of the study population

Characteristic	Total	Any use of flecainide	Any use of propafenone	Any use of sotalol	Any use of amiodarone
Number	141 500	3356	3745	23 346	10 376
Women (%)	47.2	38.7	38.7	41.1	33.7
Age, mean ± SD (years)	72.6 ± 12.9	60.9 ± 11.7	63.9 ± 11.6	66.4 ± 11.9	67.2 ± 11.1
Women, age	75.9 ± 11.9	64.9 ± 11.4	67.3 ± 11.4	70.2 ± 11.1	70.8 ± 10.0
Men, age	69.7 ± 13.1	58.4 ± 11.3	61.8 ± 11.3	63.7 ± 11.8	65.4 ± 11.2
Comorbidity					
Previous MI	8466 (5.9)	41 (1.2)	83 (2.2)	1173 (5.0)	1021 (9.8)
Ischaemic heart disease	23 000 (16.3)	212 (6.3)	404 (10.8)	3508 (15.0)	2525 (24.3)
Congestive heart failure	25 195 (17.8)	153 (4.6)	285 (7.6)	2224 (9.5)	2234 (21.5)
Other arrhythmia	7818 (5.5)	363 (10.8)	319 (8.5)	1740 (7.5)	1243 (11.9)
Cerebrovascular disease	13 297 (9.4)	90 (2.7)	122 (3.3)	1049 (4.5)	456 (4.4)
Peripheral vascular disease	2657 (1.9)	11 (0.3)	29 (0.8)	231 (0.9)	171 (1.7)
COPD	10 856 (7.7)	114(3.4)	228(6.1)	426 (1.8)	845 (8.1)
Diabetes	10 437 (7.4)	66(1.9)	135(3.6)	1002 (4.3)	697 (6.7)
Malignant condition	3437 (2.4)	22(0.7)	30(0.8)	267 (1.1)	155 (1.5)
Concomitant medical treatment					
Beta-1-selective blockers	25 434 (17.9)	501 (14.9)	526 (14.1)	4269 (18.3)	2504 (24.1)
Calcium antagonists	33 760 (23.9)	759 (22.6)	946 (25.3)	5515 (23.6)	2682 (25.9)
Digoxin	53 270 (37.7)	1017 (30.3)	1396 (37.3)	7744 (33.2)	3759 (36.2)
Warfarin	24 879 (17.6)	747 (22.3)	862 (23.0)	5045 (21.6)	2503 (24.1)
Loop diuretics	47 194 (33.4)	385 (11.5)	732 (19.6)	5065 (21.7)	3813 (36.8)
Statins	9128 (6.5)	118 (3.5)	186 (4.9)	1497 (6.4)	1175 (11.3)
Glucose lowering medication	8656 (6.1)	70 (2.1)	135 (3.6)	1002 (4.3)	555 (5.4)

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dosage from all prescriptions claimed. As amiodarone was the only AAD with a long plasma half-life and thus potential for a carryover of risk in relation to treatment switch, it was ascertained how many patients who were actually exposed to this risk. The amount was small ($n = 189$) and no deaths occurred within 3 months of amiodarone cessation. It was therefore not included as a covariate in the analyses.

Endpoint

The predefined endpoint of interest was all-cause mortality.

Statistical analyses

To strengthen the findings, three different statistical analyses were employed to estimate the potential risks associated with AAD therapy. Initially, Cox regression models with AAD treatment as time-dependent covariate were used. The time-dependent exposure variable ensured that patients were only considered at risk when receiving the medication (exposed). All models were adjusted for age, gender, calendar year, comorbidity, and concomitant medical treatment (as listed in *Table 1*). The reference group for the models were all patients not in AAD treatment, and for sensitivity analyses, AAD-treated patients out of treatment as reference were also performed. The model assumptions, linearity of continuous variables, and lack of interactions were tested and found valid. Additionally, tests of differences between the linear hypotheses of the Cox models were conducted and were shown to be significant. Patients were censored in the event of death and at the end of the study period (31 December 2004).

Secondly, a propensity score analysis was performed to enhance the accuracy of the Cox models by dividing the population into closely matched groups defined by the propensity to receive a specific AAD within 90 days conditional on the baseline covariates. Multivariate Cox models were then used to assess hazard ratios between the groups. The *C*-statistic for this model was 0.80, indicating good discrimination between treatment groups.

Thirdly, to minimize the effect of unmeasured confounders, case-crossover analyses with the use of conditional logistical regression models[12] were employed. The case-crossover analysis is based on the case-base paradigm, but instead of using matched controls the case serves as its own control in other periods than the case period. Only patients experiencing an event of interest are included in the case-crossover analysis. Among these patients, the number having medication available in the case period (which is the period immediately before the event of interest) is compared with the number having medication available in the control period (which is a period further back in time than the case period but of the same length as the case period). The case period was defined as treatment during 0–30 days prior to death and as control: two periods of 60–90 and 90–120 days prior to death were used.

All statistical calculations were performed using the SAS statistical software package, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics

The Danish Data Protection Agency approved this study (No. 2003-54-1269). Retrospective registry-based studies do not require ethical approval in Denmark.

Results

Between 1995 and 2005, 141 500 patients were discharged alive after a first-time hospitalization for AF. Baseline characteristics of the study population are shown in *Table 1*. Following discharge, a total of 40 823 (28.9%) patients claimed a prescription for an AAD. Flecainide ($n = 3356$; 2.4%), propafenone ($n = 3745$; 2.6%), sotalol ($n = 23\,346$; 16.5%), or amiodarone ($n = 10\,376$; 7:3%). A higher prevalence of male gender and younger age was present in the treatment groups compared with patients not receiving AAD therapy. Patients receiving amiodarone had the highest prevalence of comorbidity and concomitant medication compared with the other exposure groups. Conversely, patients who received class 1C AADs had a lower prevalence of comorbidity and concomitant pharmacotherapy. Of the entire cohort, 5.0% received treatment with class 1C AADs. The mean follow-up of the total study cohort was 3.2 years after discharge (SD 2.7 years).

Mean dosages of the AADs were for flecainide 205.6 mg (SD ± 56.1 mg), propafenone 411.4 mg (± 117.0 mg), sotalol 122.9 mg (± 49.7 mg), amiodarone 287.4 mg (± 87.9 mg).

The duration of treatment for patients receiving class 1C AADs was slightly longer than those treated with sotalol or amiodarone (*Table 2*).

Mortality

Between 1995 and 2005, there were 62 173 (43.9%) deaths registered (*Table 2*). There were fewer deaths ($n = 11\,080$; 27.1%) in the treatment groups compared with the entire

Table 2 Mean daily dosages, average duration of follow-up, and time in treatment

	Number of patients	Mean dosage (mg)	Average duration of follow-up (year)	Average duration of treatment (year)	All deaths during follow-up (%)	Deaths during treatment (%)	Deaths within 30 days of initiating treatment (%)	Annualized mortality rates (per year per 100 person years)
Flecainide	3356	205.6 ± 56.1	5.8	2.4	492 (14.7)	160 (4.8)	14 (0.4)	2.54
Propafenone	3745	411.4 ± 117.0	5.5	2.3	877 (23.4)	342 (9.1)	20 (0.5)	4.25
Sotalol	23 346	122.9 ± 49.7	5.2	1.7	6464 (27.7)	3145 (13.5)	192 (0.8)	5.29
Amiodarone	10 376	287.4 ± 87.9	4.2	1.6	3247 (31.3)	1779 (17.1)	212 (2.0)	7.42
Total cohort	141 500				62 173 (43.9)			

All deaths during follow-up. Deaths during treatment and within 30 days of initiating treatment. Annualized mortality rates (deaths per year per 100 person years).

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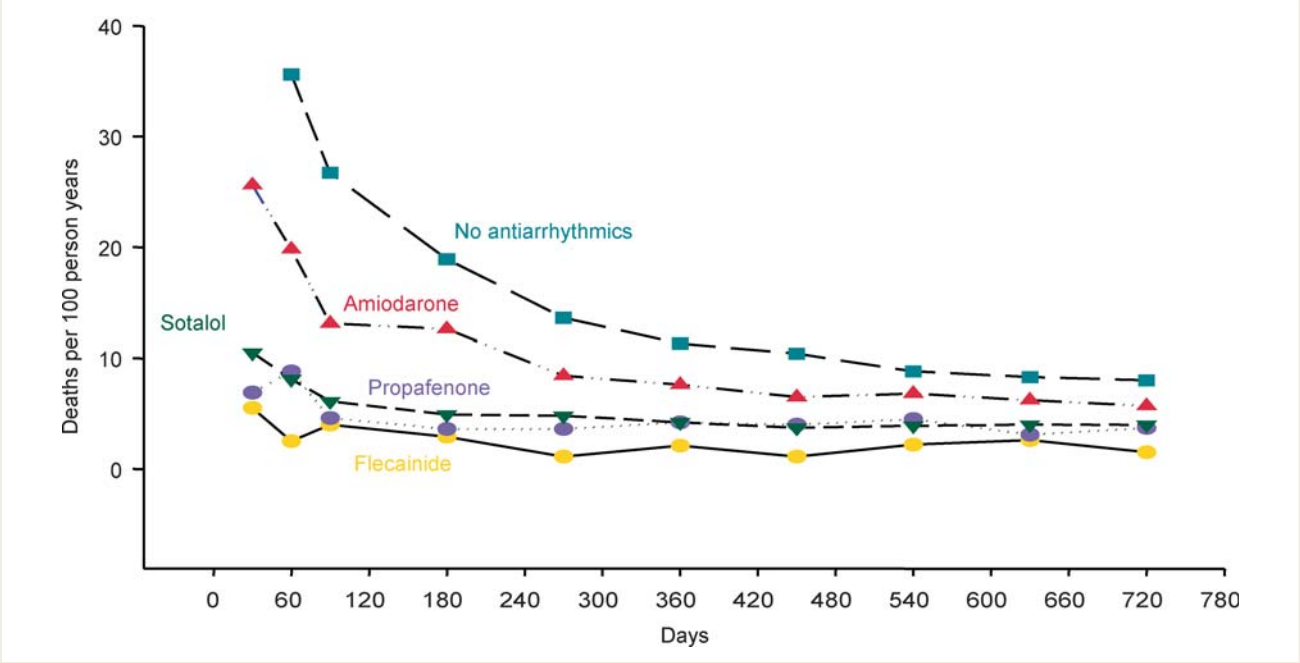

Figure 1 Incidence rates for deaths in all treatment groups and in the population receiving no antiarrhythmics. Time starts from the day of prescription claim. For patients receiving no antiarrhythmic drugs, time starts 60 days following discharge.

Table 3 Risk of death assessed by the three modalities: Cox analyses with the study drug as time-dependent variable, propensity score matching by propensity to receive study drug, and case-crossover analyses with 0–30 days prior to death being case period and 60–90 and 90–120 days prior to death being control periods

Exposure group	Cox analyses with time-dependent variables [Hazard ratio (95% CI)]	Propensity analyses [Hazard ratio (95% CI)]	Case-crossover analyses [Hazard ratio (95% CI)]
Flecainide	0.38 (0.32–0.44)	0.55 (0.46–0.65)	0.32 (0.18–0.59)
Propafenone	0.65 (0.58–0.71)	0.61 (0.41–0.91)	0.62 (0.40–0.96)
Sotalol	0.65 (0.63–0.67)	0.62 (0.52–0.73)	0.36 (0.29–0.42)
Amiodarone	0.94 (0.89–1.00)	0.94 (0.74–1.17)	0.81 (0.70–0.94)

population. Very few deaths occurred within 30 days of treatment initiation and deaths in the treatment groups occurred most frequently after the patients had stopped taking the medication and were thus unexposed to the AAD. Annualized mortality rates were 2.54, 4.25, 5.29, and 7.42 per year per 100 person years for flecainide, propafenone, sotalol, and amiodarone, respectively (*Table 2*). Incidence rates for deaths demonstrated significantly lower rates in all the treatment groups over time compared with the population receiving no AAD therapy (*Figure 1*). In the multivariable Cox proportional-hazard analysis, the risk of death was significantly lower in all treatment groups except for the amiodarone group, where the risk was not different from those not receiving AADs (*Table 3*). The propensity-score matched analysis and the case-crossover models confirmed these findings (*Table 3*).

Discussion

This study examined the cardiovascular risk associated with AAD treatment in an unselected population of patients discharged after first hospitalization for AF. The main findings were that AAD therapy was not associated with increased risk of death in patients with AF. Deaths occurring in the treatment groups were fewer than observed in the population not receiving AADs. Also, deaths occurring in the treatment groups, particularly for the flecainide and propafenone groups and partly for the sotalol recipients, were predominantly observed after AAD therapy had been discontinued. Additionally, very few deaths were observed within 30 days of treatment initiation where fatalities in patients susceptible to the proarrhythmic effects of AADs might be highest. Somewhat unexpectedly, there were relatively large percentages

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of patients with IHD or CHF receiving treatment with class 1C AADs (*Table 1*), although this did not seem to affect the outcome.

Our study thereby indicates no increased mortality among patients selected to receive this treatment as recommended by international guidelines.[13] These findings remained consistent in several different statistical models.

International guidelines[13] recommend sotalol, flecainide, and propafenone as first-line drugs when attempting to maintain sinus rhythm in AF patients without underlying structural heart disease. However, as previously documented, in the Danish population prescription of these drugs has declined rapidly over the last years in lieu of conventional beta-blockers.[6] This shift may partly derive from the results of studies such as CAST[1] and SWORD[2] where treatment with 1C AADs and sotalol in patients with structural heart disease was clearly associated with increased mortality. However, for patients with AF without cardiac comorbidity, an increased mortality risk associated with the use of AADs has never been shown. Nichol *et al.*[14] evaluated the effectiveness of AAD therapy to maintain sinus rhythm in patients with AF in a large meta-analysis, but while containing many relevant randomized trials, it lacked the statistical power to evaluate the possible effect on mortality when using AADs in the setting of AF.

In a substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), which examined the cause-specific modes of death, no differences were found between the rate- and rhythm-control groups concerning fatal cardiac outcomes.[15] Notably, there were no differences in the numbers of arrhythmia-related deaths between the groups. In another AFFIRM substudy evaluating the risk of proarrhythmic events in the rhythm control group, a low incidence of events and a prognostic indicator being left ventricular ejection fraction $<40\%$ was demonstrated.[16]

Results from our study corroborate the AFFIRM findings in a large unselected population as we found no increased risk of death associated with AAD treatment. It should be noted however that there are differences in the baseline characteristics in the rhythm arm of the AFFIRM population compared with the segment of our population receiving treatment with 1C AADs and sotalol. The AFFIRM patients were older and had a much higher prevalence of coronary heart disease as well as history of CHF. It is also of interest to note that the few instances of arrhythmic events in the rhythm-control group indicate that an appropriate AAD therapy was selected by physicians. We believe this also applied to our population considering that the lower mortality risk in the treatment groups persisted even when compared with similar patients in the no-AAD population as demonstrated in the propensity analyses. This could be attributed to a hitherto unknown mortality benefit associated with the flecainide, propafenone, or sotalol use, but more likely it reflects an underlying selection bias whereby the treating physician identifies the patients in whom AAD treatment is appropriate by factors not apparent from the registry data. This could also represent a reluctance to prescribe AAD treatment even in patients where the benefits are likely to outweigh the risks. This bias also includes the fact that any deterioration of the patient is likely to cause discontinuation of antiarrhythmic therapy. But the important finding, as previously mentioned, is the lack of increased mortality risk in patients receiving AAD treatment. In light of the AFFIRM results where rhythm- and rate-control strategies were considered equal in terms of mortality, a shift in clinical practice towards more rate control is to be expected in elderly asymptomatic AF patients, especially given the trend towards a higher mortality in the rhythm-control arm driven by the non-cardiovascular deaths. In subsets of AF patients with concomitant severe CHF, a recent study has also failed to demonstrate superiority of rhythm control, and attempting rhythm control in these patients with newer and perhaps promising AADs such as dronedarone has been shown to actually increase mortality.[5,17] However, for younger symptomatic AF patients without structural heart disease, rate control may be associated with significantly poorer quality of life, making rhythm control, and thereby AAD-therapy the most viable treatment option. Our study indicates that for these patients such a strategy imposes no greater risk.

Strengths and limitations

The main strengths of this study are the large study cohort in an unselected patient population, the completeness of the data and the inclusion of nationwide data including the prescription practice of all hospitals in Denmark. Thereby, the study avoids selection bias such as only including certain age groups, groups of certain socioeconomic status, certain hospitals, or participants in particular health insurance plans. To avoid immortal time bias where the drug-treated patients are immune to events until first prescription claim, Cox proportional-hazards analyses with a time-dependent definition for the drug exposure were used.

The main limitation is the retrospective non-randomized nature of the study. Detailed information about important factors such as biochemical parameters, family history, drug allergies, smoking, and physician assessed level of compliance to a particular treatment cannot be obtained from these administrative registries, and the adjustment for comorbidity may be insufficient. Another main bias is physicians' awareness of the hazard of AAD treatment, which is evident from the demographic data where many high-risk patients were never given AAD treatment. Furthermore, physicians are likely to discontinue treatment if the patient's condition worsens which presumably is the most likely explanation why most fatalities occur after discontinuation of therapy.

Conclusions

In a large unselected population-based cohort of patients discharged with the first-time AF and subsequently treated with flecainide, propafenone, sotalol, or amiodarone, we found no increased risk of death. This indicates adequate patient selection by the treating physicians from a safety perspective. Our findings corroborate the recommendations outlined in current international guidelines for the treatment of AF. Furthermore, this study underscores the importance of appropriate risk stratification and individual patient evaluation before initiating AAD therapy in AF patients.

Conflict of interest: none declared.

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